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Jordan, S., Morris, J., Davies, G.I., Tucker, D., Thayer, D.S., Luteijn, J.M., Morgan, M., Garne, E., Hansen, A.V., Klungsøyr, K., Engeland, A., Boyle, B., & Dolk, H. (2016). Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in Pregnancy and Congenital Anomalies: analysis of linked databases in Wales, Norway and Funen, Denmark. *PLoS ONE*, 11(12), [e0165122]. <https://doi.org/10.1371/journal.pone.0165122>

Published in:
PLOS ONE

Document Version:
Peer reviewed version

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Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in Pregnancy and Congenital Anomalies: analysis of linked databases in Wales, Norway and Funen, Denmark

Short title: SSRIs and Congenital Anomalies

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key words: SSRIs, congenital anomalies, congenital heart defects, longitudinal cohorts

Abstract

Background

Hypothesised associations between in utero exposure to selective serotonin reuptake inhibitors (SSRIs) and congenital anomalies, particularly congenital heart defects (CHD), remain controversial. We investigated the putative teratogenicity of SSRI prescription in the 91 days either side of first day of last menstrual period (LMP).

Methods and Findings

Three population-based EUROCAT congenital anomaly registries- Norway (2004-2010), Wales (2000-2010) and Funen, Denmark (2000-2010) - were linked to the electronic healthcare databases holding prospectively collected prescription information for all pregnancies in the timeframes available. We included 519,117 deliveries, including foetuses terminated for congenital anomalies, with data covering pregnancy and the preceding quarter, including 462,641 with data covering pregnancy and one year either side. For SSRI exposures 91 days either side of LMP, separately and together, odds ratios with 95% confidence intervals (ORs, 95%CI) for all major anomalies were estimated. We also explored: pausing or discontinuing SSRIs preconception, confounding, high dose regimens, and, in Wales, diagnosis of depression. Results were combined in meta-analyses.

SSRI prescription 91 days either side of LMP was associated with increased prevalence of: all major anomalies combined (3.09% [400/12,962] vs. 2.67% [13,536/506,155] OR 1.09, 0.99-1.21, short of statistical significance; severe congenital heart defects (CHD)[†] (34/12,962 [0.26%] vs. 865/506,155 [0.17%] OR 1.50, 1.06-2.11); the composite adverse outcome of 'anomaly or stillbirth' (473/12962, 3.65% vs. 15829/506,155, 3.13%, OR 1.13, 1.03-1.24). Adjusting for socio-economic status left ORs largely unchanged. The prevalence of anomalies and severe CHD was reduced when SSRI prescriptions were stopped or paused preconception, and increased when >1 prescription was recorded. The dose-response relationship between severe CHD and SSRI dose (meta-regression OR 1.49, 1.12-1.97) was consistent with SSRI-exposure related risk. Analyses in Wales suggested no associations between anomalies and diagnosed depression.

1 **Conclusion**

2 The additional absolute risk of teratogenesis associated with SSRIs, if causal, is small.

3 However, the high prevalence of SSRI use augments its public health importance, justifying
4 modifications to preconception care.

5 299 words

6 †Severe CHD, as defined by EUROCAT guide 1.3 (EUROCAT 2005)

7

1 Introduction

2 Exposure to selective serotonin reuptake inhibitors (SSRIs) during the first trimester of
3 pregnancy, including the crucial period of organogenesis (the first 49 days after
4 implantation)[1], affects 4% of pregnant women in the USA[2] and UK[3]. SSRI prescribing
5 indications, mainly depression, panic, obsessive-compulsive or social anxiety disorders, and,
6 for fluoxetine, bulimia nervosa, are not always recorded [3]. SSRIs, particularly fluoxetine
7 and citalopram, and their metabolites, cross the placenta[4], and appear in cord blood[5,6];
8 their presence in amniotic fluid prolongs foetal exposure. SSRIs, and some other
9 antidepressants, act on the crucial serotonin transporter (SERT, aka 5HTT, SLC6A4, OMIM
10 182138), which regulates the synaptic concentration of serotonin (5HT) in many tissues,
11 including the placenta[7]. The resultant increased bioavailability of serotonin affects
12 vasoconstriction and coagulation or bruising [6,8,9], cardiac morphogenesis [10,11], CNS
13 development[6] gastrulation, laterality and craniofacial development[10], conferring
14 biological plausibility on reported associations between SSRI exposure during organogenesis
15 and certain congenital anomalies.

16
17 The full impact of exposure to SSRIs *in utero* is incompletely understood, and not all
18 problems initially suspected [12] have been confirmed by further investigation. Some[13-
19 16], but not all[17-22], observational studies indicate significant associations between SSRI
20 exposure during organogenesis and all congenital anomalies combined. Risks may be
21 confined to specific SSRIs and specific anomalies[23,24]. However, the literature offers no
22 consistency: paroxetine is implicated in some studies[24],[25], and fluoxetine[24,26,27],
23 citalopram/ escitalopram[17,27] and sertraline[17,28] in others. Meta-analyses[26,29,30]
24 and analysis of 12 EUROCAT registries[31] indicate an overall association between SSRI
25 exposure and congenital heart defects (CHD) ; however, there is no
26 consensus[21,22,29,32,33]. The most persistent associations relate to paroxetine exposure
27 and CHD[22,24,27,30,31], particularly at doses >25mg/day[34]. Epidemiologists also report
28 increased risks of: neural tube defects[33,35], ano-rectal stenosis/ atresia[23], gastroschisis,
29 omphalocele[35], renal dysplasia, hypospadias[27], limb reduction[23], talipes equinovarus
30 (clubfoot)[23], craniosynostosis[35], anomalies of the eye[18], ear, face[36], respiratory[36]
31 and digestive tracts[15,24].

To investigate the putative teratogenicity of SSRIs, three countries from the pan-European congenital anomalies registry network[37,38] were linked with healthcare databases. We aimed to examine any associations between major congenital anomalies and: prescription of antidepressant medicines in the 91 days either side of the 1st day of last menstrual period (LMP); high dose SSRI regimens; confounding; pausing or stopping SSRI pharmacotherapy before pregnancy; and diagnosed, unmedicated depression.

Methods

Three population-based cohorts containing prospectively collected linked prescription data were interrogated using a common protocol. Ethical and data access approvals were obtained for each country from the relevant governance infrastructures (see acknowledgements).

Settings

Three congenital anomalies registries that contribute to EUROCAT[37,39] were linked with prescription and healthcare databases covering their source populations[40,41]. We examined anonymised linked routinely collected data on congenital anomalies, primary care prescribing (Wales) or dispensing (Denmark, Norway), concurrent maternal diagnoses and demographic indicators from:

1. Denmark's Medical Birth registry, Danish national Prescription and Patient registers, Statistics Denmark[42] and the Funen, Denmark (Odense) EUROCAT register.
2. Norway's Medical Birth Registry, containing all EUROCAT cases, linked to the National Prescription Database and the National Education Database[43,44].
3. Wales' health and social care linked electronic databank (the Secure Anonymised Information Linkage [SAIL]). SAIL links primary care records, including prescriptions, for ~40% of the population to the Office of National Statistics births and deaths register, the National Community Child Health Database (NCCHD), the Patient Episode Database for Wales and CARIS (Congenital Anomaly Register and Information Service for Wales). All general practices were invited to participate, without payment, and ~40% had done so in 2014[45,46].

Databases were linked by trusted third parties (Statistics Denmark, Statistics Norway in conjunction with the National Prescription Database, NHS Wales Informatics Service) using unique personal identifiers, which remained undisclosed to researchers, ensuring anonymity.

Study Population

The study population included all fetuses and infants who 1) would have appeared in the EUROCAT registries had they been diagnosed with a major congenital anomaly, 2) had linked maternal prescription data, and 3) whose birth outcome was either live birth or still birth/ late foetal death after 20 weeks (24 weeks in Wales) or termination of pregnancy for foetal anomaly (TOPFA) recorded in the EUROCAT register. Deliveries from 1st January 2000 to 31st December 2010 were included in Wales and Denmark. In Norway, all pregnancies with date of LMP after April 1st 2004 and ending before 31st December 2010 were included, to co-incide with the start of the prescription database. In Wales, infants were included where the associated maternal ID was in the geographical areas that could be linked with the primary care dataset and the record was complete[41]. We prepared 2 datasets with an inclusion criterion relating to the woman's time on the linked database with prescription information:

1. 91 days before LMP to delivery (birth or TOPFA) (main analysis)
2. 365 days before LMP to 365 days after delivery

Information on start of pregnancy was obtained from ultrasound scan data recorded in the Medical Birth Registers of Norway and Denmark (MBRN, MBRD), and the NCCHD for Wales [41]. Representivity was checked in Denmark and Wales by comparing socioeconomic status (SES) with national populations.

Exposure

Exposure was defined as one or more prescription for an antidepressant issued (Wales) or dispensed (Norway & Denmark) 91 days either side of the first day of LMP. We based our timeframe on prescription duration (typically 90 days) and relevant pharmacokinetic parameters: for example elimination of the active metabolite of fluoxetine can take ~40 days in adults[47], and longer in the embryo or foetus[11]. Antidepressants were investigated according to anatomical, therapeutic, chemical (ATC) classification [48]: 1) grouped a) all SSRIs (NO6AB); b) all antidepressants (NO6A); 2) as individual SSRIs, fluoxetine, citalopram, paroxetine, sertraline, escitalopram, fluvoxamine. Where more than

one SSRI had been prescribed, exposure was not allocated to either SSRI; women switching were retained as SSRI exposed. Where non-SSRI antidepressants were co-prescribed, exposure was classified according to the SSRI. Denmark supplied data on SSRIs only.

Dose was calculated from tablet and capsule sizes, to avoid missing data. We classified high dose exposure as prescription of: 60mg fluoxetine, 40mg citalopram, 30mg paroxetine, 100mg sertraline, 20mg escitalopram, based on tablet/ capsule sizes quoted in the British National Formulary (BNF)[49]. Smaller tablets and capsules were classified as 'other dose' (low or medium).

Outcomes

Major congenital anomalies were classified according to the EUROCAT standard subgroups, as defined in EUROCAT Guide 1.3, chapter 2.2 [37]. Severe CHD was defined as ICD10 codes: Q200 (common arterial trunk), Q203 (discordant ventriculoarterial connection), Q204 (double inlet ventricle), Q212 (atrio-ventricular septal defect), Q2121 (primum atrial septal defect [ASD]), Q213 (tetralogy of Fallot), Q220 (pulmonary valve atresia), Q224 (tricuspid stenosis or atresia), Q225 (Ebstein's anomaly), Q226 (hypoplastic right heart), Q230 (stenosis or atresia of aortic valve), Q234 (hypoplastic left heart), Q251 (co-arcuation of aorta), Q262 (total anomalous pulmonary venous connection). Patent ductus arteriosus in pre-term infants was not included as CHD. Minor anomalies are not recorded in EUROCAT, and not investigated. Congenital anomaly cases, diagnosed within the 1st year of life, irrespective of mother's time on database, were as reported to EUROCAT: October 2014 (Wales), February 2012 (Denmark), February 2014 (Norway). We excluded, from the main analysis, subjects with anomalies of chromosomal (EUROCAT subgroup al88) or genetic (al104, al105 & al108) aetiology, including sequences[37].

We analysed as prior hypotheses associations between SSRI prescription and 10 pre-specified anomalies identified from the literature as associated with SSRI exposure[31]: CHD, severe CHD, neural tube defects, ano-rectal atresia/stenosis, renal dysplasia, craniosynostosis, hypospadias, including 3 anomalies associated with vasoconstriction (limb reduction, abdominal wall defects (gastroschisis and omphalocele) [50,51], and talipes

equinovarus[52]. The composite outcomes, all major anomalies combined and major congenital anomalies or stillbirth, were based on the ICH (International Conference on Harmonisation) definition of serious adverse events[53].

Confounding

To minimise **confounding by co-exposure**, we achieved a relatively homogeneous population by excluding infants: 1) with EUROCAT coding[37] indicating known teratogenic syndromes (EUROCAT subgroups al82-84, al86) 2) exposed to medicines more closely associated with congenital anomalies than SSRIs during the 91 days either side of 1st day of LMP: anti-epileptic drugs (AEDs) (N03)[54]; coumarins (B01AA), mainly warfarin[55]; insulins (A10A)[56]. We examined, but did not exclude, SSRI exposed cases for: 1) exposure to other potentially teratogenic prescription medicines 91 days either side of 1st day of LMP: systemic isotretinoin (D10BA); angiotensin converting enzyme inhibitors or angiotensin II blockers (C09); lithium (N05AN); benzodiazepines (N05BA); first generation antipsychotics (N05AA through N05AG); second generation antipsychotics (N05AH, N05AL, N05AX); carbimazole (H03BB); thyroxine (N03AA); medicines rarely prescribed in primary care but associated with anomalies: aminoglycosides, ergot derivatives, lindane, gold salts, penicillamine, methotrexate, chloroquine, radiopharmaceuticals[57]; 2) heavy alcohol use and substance misuse (Wales only); 3) maternal conditions indicating that the woman might not be considered to be from the normal healthy population: hospital admission for cancer; thyroid disorders; phenylketonuria; maternal congenital anomalies[58]; 4) maternal siblings with anomalies.

To explore **confounding by indication** (usually depressive illness [59]) we investigated whether women who discontinued prescriptions before the time when a biological effect would be expected (91 days before LMP) had similar risks to those receiving SSRI prescriptions during the vulnerable period (91 days either side of LMP). Those who discontinued were divided into those who did and did not resume prescriptions within a year of delivery. We defined:

- ‘paused SSRI exposure’ as ≥ 1 prescription during the 3-12 months before pregnancy plus ≥ 1 prescription during the year after pregnancy and no prescriptions during both the quarter preceding pregnancy and pregnancy.

- discontinuation (stopping) as ≥ 1 prescription during the 3-12 months before pregnancy and no further prescriptions throughout the quarter preceding pregnancy, pregnancy, and the first year after delivery.

As a sensitivity analysis, we repeated this analysis defining exposure as >1 prescription in each time period (1 year to 91 days before LMP, LMP \pm 91 days, 1 year after delivery).

Statistical Analysis

For each country separately, we explored associations between pre-specified outcomes (above) plus each congenital anomaly subgroup and all SSRIs, individual SSRIs, and all antidepressants. For exploration of individual SSRIs, those exposed to other SSRIs were excluded from the analysis. The odds of exposure for subjects with and without each anomaly were compared by calculating odds ratios (ORs) with Cornfield 95% confidence intervals (95% CI). For anomalies with >2 exposed cases in the 3 countries combined, meta-analysis of country-specific effects was undertaken, using the Mantel Haenszel method, with alternative continuity corrections, described by Sweeting *et al.* (2004)[60]. Heterogeneity was assessed using the I^2 statistic. We repeated the analysis of all SSRIs excluding infants exposed to any non-SSRI antidepressants (e.g. SNRIs, tricyclic antidepressants); data availability restricted this to Norway & Wales. When evaluating associations other than the 10 pre-specified signals, we applied Simes' multiple testing procedure to control the false discovery rate to 5% (FDR) [61, 62]. For 'all anomalies', 'anomalies + stillbirths', CHD, and severe CHD, confounding by smoking and socio-economic status were explored in separate fixed effects logistic regression models. The SSRI dose-response relationships for all anomalies, CHD, severe CHD and 'anomaly or stillbirth' were explored for zero, 'other' and high doses, using random effects meta-regression. Analyses were performed using Stata 12.1[63].

Wales sub-cohort

In Wales, confounding by indication was further explored by investigating depression and unmedicated depression, defined as a diagnosis of depression in the woman's record any time during her registration with a participating GP before the end of the first trimester, but

no antidepressant prescribed in the 91 days either side of the 1st day of LMP. We explored associations between prespecified anomalies [31], and socioeconomic status (as Townsend fifth), smoking, antipsychotics, substance misuse and heavy drinking in *a posteriori* subgroups, to generate hypotheses for future work. Substance misuse often coincides with heavy drinking, and *vice versa*, and we combined the two exposures. We took recorded diagnoses of misuse at any time as indicative of a problem likely to recur. Analyses were undertaken in SPSS version 20 for Windows[64].

Results

The population comprised 519,117 subjects (foetuses and infants): 346739 from Norway; 56447 from Funen, Denmark; 115931 from Wales (S1a-S1c Tables, Fig 1). In Wales, the included population were less deprived than the rest of Wales [41]. There were no significant demographic differences between Funen County and ‘all Denmark’. Exposure to SSRIs and antidepressants and prevalence of non-chromosomal, non-genetic congenital anomalies were higher in Wales than the Scandinavian countries (Table 1). Norway had the lowest prescription rates for paroxetine, >1 type of SSRI and high doses (Table 2).

Figure 1. Participant Flow diagram

Table 1. Summary of SSRI and antidepressant exposures and congenital anomaly (CA) prevalence in 3 countries: Denmark, Norway, Wales

	Total Number			SSRI exposed ^a LMP±91 days ^b				Antidepressant exposed LMP±91 days			
	Pop (N)	CA Cases (N)	Prevalence of CA (%)	Pop (N)	CA Cases (N)	% of population exposed	Prevalence of CA (%)	Pop (N)	CA Cases (N)	% of population exposed	Prevalence of CA (%)
Denmark	56,447	1288	2.28	1169	33	2.07	2.82	no data	no data		
Norway	346,739	8991	2.59	5451	149	1.57	2.73	7619	198	2.20	2.60
Wales	115,931	3657	3.15	6342	218	5.47	3.44	8019	264	6.92	3.29
total	519,117	13,936	2.68	12,962	400	2.50	3.09	15,638	462	3.01	2.95

Notes: ^aExposure defined as >0 prescriptions of SSRIs at any dose with or without co-prescriptions

^bLMP±91 days represents 91 days either side of 1st day of LMP

Exclusions: 1) chromosomal, genetic, teratogenic anomalies; 2) exposure during the 91 days either side of LMP to: insulin, AEDs, coumarins

The 3 countries have similar population sizes and life expectancies, but differ in: GDP *per capita* (Wales \$23.90k [65] Denmark \$50.46, Norway \$72.96K[66]; the proportion of children living in poverty, defined as <60% median household income (Wales 28% [[67], Denmark 7% and Norway 8% [68]); and unemployment rates (Wales 5.3%, Denmark 3.9% and Norway 3.4%)[65,66], (2006 data). Much of Wales is an EU Convergence area [69].

Table 2. SSRI exposure 91 days either side of LMP^a by individual SSRI^b and dose: 3 countries

		Denmark		Norway		Wales		Summed	
		Number exposed	% total exposed	Number exposed	% total exposed	Number exposed	% total exposed	Number exposed	% total exposed
Population		56,447		346,739		115,931		519,117	
Exposed to any SSRI		1169	100	5451	100	6342	100	12,962	100
SSRI	Fluoxetine	155	13.26	509	9.34	1937	30.54	2601	20.07
	Citalopram	478	40.89	867	15.91	2683	42.31	4028	31.08
	Paroxetine	106	9.07	325	5.96	638	10.06	1069	8.25
	Sertraline	175	14.97	804	14.75	395	6.23	1374	10.60
	Escitalopram	138	11.80	2750	50.45	348	5.49	3236	24.97
	Exposed >1 SSRI	117	10.01	196	3.60	341	5.38	654	5.05
Dose	High	255	21.81	364	6.68	810	12.77	1429	11.02
	Other	914	78.19	5087	93.32	5532	87.23	11,533	88.98

Notes: ^aExclusions and exposures as Table 1.

^bFluvoxamine: 28 exposures and 0 exposed cases were identified, see S2a Table.

1 Prevalence of most, not all, **major congenital anomalies** was higher amongst those exposed
2 to **SSRIs** than those unexposed (Tables 3, S2a, S3). Anomalies occurred in 3.09% of those
3 exposed to ≥ 1 SSRI prescription 91 days either side of 1st day of LMP, exceeding the
4 prevalence in the unexposed populations (2.67%), but 95% confidence intervals included
5 one (OR 1.09, 0.99-1.21, Table 3). Exposure was associated with the composite adverse
6 outcome 'any major anomaly or stillbirth' (OR 1.13, 1.03 - 1.24, [Table 3], number needed to
7 harm [NNH] 192, 95% CI 118-512), severe CHD (OR 1.50, 1.06-2.11, NNH 1094, 555-38,141),
8 and abdominal wall defects (OR 1.75, 1.07-2.88, NNH 1629, 832-39,830).

9 We did not confirm associations with all CHD, neural tube defects, talipes equinovarus,
10 hypospadias, renal dysplasia, ano-rectal atresia/stenosis, limb reduction or craniosynostosis.
11 The association with gastroschisis did not reach statistical significance (OR 1.92, 0.97-3.78,
12 based on 9 exposed cases). Positive associations involved all individual SSRIs, and included
13 paroxetine with all CHD and ventricular septal defect (VSD), fluoxetine with neural tube
14 defects and citalopram with hypospadias. Escitalopram was associated with talipes
15 equinovarus and abdominal wall defects (S3 Table). For **all antidepressants**, differences in
16 prevalence of major anomalies between exposed and unexposed were less marked and 95%
17 confidence intervals included one (OR 1.03, 0.93 - 1.13) (S2b, S3 Tables). There were <3
18 exposed cases for 27/75 anomalies (S2a and S2b Tables). When Simes' False Discovery Rate
19 procedure was applied, no associations reached the 5% false discovery rate significance level
20 threshold, including those with diaphragmatic hernia and syndactyly (S4 Table). When data were
21 re-analysed in Norway and Wales with those **co-prescribed other antidepressants excluded**,
22 prevalence rates and ORs changed little, and the association with renal dysplasia increased
23 (S3 Table). Heterogeneity was low for most outcomes, except CHD and severe CHD (Table
24 3). The NNH for severe CHD varied: 298 (172-11,111) in Denmark, 854 (400-14,286) in
25 Wales, and there was no association in Norway.

Table 3. SSRI (N06AB) exposures 91 days either side of LMP^a and outcomes^b based on signals: 3 countries

	Denmark				Norway				Wales				Summed					
	exposed n=1169		unexposed n= 55,278		Exposed n=5451		unexposed n= 341,288		exposed n= 6342		Unexposed n= 109,589		exposed n= 12962		unexposed n= 506,155		Meta-analysis	
	n	%	N	%	n	%	N	%	n	%	n	%	n	%	n	%	OR, 95% CIs	I ²
Anomaly or stillbirth	40	3.42	1586	2.87	185	3.39	10412	3.05	248	3.91	3819	3.48	473	3.65	15829	3.13	1.13 (1.03-1.24)	0
All Anomalies	33	2.82	1255	2.27	149	2.73	8842	2.59	218	3.44	3439	3.14	400	3.09	13,536	2.67	1.09 (0.99 - 1.21)	0
Neural Tube Defects	<5		55		6	0.11	271	0.08	10	0.16	123	0.11	17-20	0.14	449	0.09	1.43 (0.89 - 2.30)	0
CHD	16	1.37	447	0.81	44	0.81	3027	0.89	61	0.96	1029	0.94	121	0.93	4503	0.89	1.03 (.86 - 1.24)	55.66
Severe CHD	6	0.51	98	0.18	9	0.17	567	0.17	19	0.30	200	0.18	34	0.26	865	0.17	1.50 (1.06 - 2.11)	51.36
Abdominal wall defects ^{c,e}	<5		18-21		6	0.11	174	0.05	8	0.13	80	0.07	15-18	0.12	275	0.05	1.92 (1.13 - 3.24)	0
Talipes equinovarus ^c	<5		73-76		12	0.22	473	0.14	11	0.17	190	0.17	24-27	0.19	736-9	0.15	1.20 (0.79 - 1.8)	0
Hypospadias	<5		119-122		12	0.22	726	0.21	21	0.33	295	0.27	34-37	0.28	1140-1143	0.23	1.15 (0.82 - 1.61)	0
Ano-rectal atresia and stenosis ^d													7	0.06	150	0.03	1.85 (0.86 - 3.96)	0
Renal Dysplasia ^d													10	0.08	177	0.03	1.57 (0.83 - 2.98)	0
Limb reduction ^{c,d}													6	0.05	254	0.05	0.81 (0.36 - 1.82)	0
Craniosynostosis ^d													4	0.03	115	0.02	0.81 (0.3 - 2.21)	0

Notes to table: We are unable to disclose numbers 1-4. Accordingly, we are only able to supply ranges for related values. Where >1 country had <5 exposed cases we are unable to report numbers for individual countries.

^aExclusions and exposures as Table 1.

^bAnomalies selected for reporting based on background literature[31].

^c Anomalies associated with vasoconstriction [50]

^d Data from each country were analysed separately, but low numbers preclude reporting by country for these anomalies plus gastroschisis and omphalocele.

^e Abdominal wall defects (gastroschisis, Q792, omphalocele, Q793 and other wall defects, Q795) were combined to achieve sufficient numbers to report, considering their purported common aetiology (vasoconstriction of the omphalomesenteric artery) [70] [71].

Further information is in Tables S2a, S2b (including numbers and %s of cases), S3 and EMC 2015 supplementary tables S3 and S4 [41]

Analyses of SNRI exposure in Wales and Norway are in Table S2b and EMC (2015) [41] (Denmark was unable to supply data on SNRIs.) There were 1448 SNRI exposures and 46 exposed cases (3.18%) (OR 1.14, 0.85 - 1.53). No associations with anomalies listed above where 95% confidence intervals did not include one were identified.

Rubrics indicate 95% confidence intervals exclude 1.

CHD represents congenital heart defect.

Dose-response

A minority were exposed to prescriptions for high doses of SSRIs (Table 2). Meta-regression for the 3 categories (high, other and zero dose) indicated significant associations for severe CHD and 'anomaly or stillbirth' and non-significant trends for all anomalies and CHD (Table 4). Denmark had a higher proportion of both high dose exposures and severe CHD.

Table 4. High Dose exposure^a and 'all anomalies', CHD, severe CHD, 'Stillbirth or Anomaly': 3 countries

	High dose LMP±91 days n=1429		Other dose LMP±91 days n=11,533		Unexposed LMP±91 days n=506,155		Meta regression ^b
	N	% of exposed	N	% of exposed	N	% of exposed	OR (95%CI)
Anomaly or stillbirth	53	3.71	420	3.64	15,829	3.13	1.10 (1.02-1.20)
All anomalies	43	3.01	357	3.10	13,525	2.67	1.08 (0.99-1.17)
CHD	18	1.26	103	0.89	4495	0.89	1.06 (0.91-1.24)
Severe CHD	7	0.49	27	0.23	864	0.17	1.49 (1.13-1.97)

Notes: ^aExclusions and exposures as Table 1.

^bNo measure of heterogeneity is available. ORs quoted represent category increases in dose.

Confounding by co-exposure

Adjusting for smoking and SES made little difference to ORs. Adjusting for smoking reduced the numbers of exposed cases, due to missing data disproportionately affecting the cases (S1a Table) and uncertainty over ex-smokers, and widened confidence intervals to include one (Table 5). Checks indicated that: 52 of the 400 exposed cases had been exposed to prescription medicines identified as potentially teratogenic (listed under 'confounding'), benzodiazepines (21) thyroxine (13), antipsychotics first generation (9), second generation (5), angiotensin converting enzyme inhibitors (3), lithium (1), and 0 for all other exposures; 30 were exposed to maternal ill-health; 14 had siblings in the dataset with anomalies, and 12 had mothers with an anomaly recorded. Of the 34 exposed severe CHD cases, 6 were also exposed to potential teratogens of varying potency, benzodiazepines (2 or <5), thyroxine (2), lithium (1), and first generation antipsychotics (1), 2 were exposed to maternal ill-health and none had maternal siblings or mothers with any congenital anomaly.

Table 5, Congenital anomalies and stillbirths and SSRI exposure LMP±91 days^a: analyses adjusted for smoking and socio-economic status (SES)

	Adjusted analysis		Unadjusted analysis		Number of exposed cases	
	Meta OR (95% CI)	I ²	Meta OR (95% CI)	I ²	adjusted analysis	Un-adjusted analysis ^c
Outcome adjusted for smoking						
All Anomalies	1.08 (0.97-1.20)	0	1.09 (0.99 - 1.21)	0	366	400
CHD	1.00 (0.82-1.21)	46.4	1.03 (0.86 - 1.24)	55.66	108	121
Severe CHD	1.43 (0.99-2.07)	47.9	1.50 (1.06 - 2.11)	51.36	30	34
Anomaly or stillbirth	1.12 (1.01-1.23)	0	1.13 (1.03-1.24)	0	433	473
Outcome adjusted for SES ^b : lowest vs. the rest						
All Anomalies	1.09 (0.98-1.21)	0	1.09 (0.99 - 1.21)	0	398	400
CHD	1.03 (0.85-1.23)	25.1	1.03 (0.86 - 1.24)	55.66	120	121
Severe CHD	1.47 (1.04-2.08)	23.6	1.50 (1.06 - 2.11)	51.36	34	34
Anomaly or stillbirth	1.12 (1.02-1.23)	0	1.13 (1.03-1.24)	0	471	473

Notes: ^aExclusions and exposures as Table 1.

^bSES: years in education in Denmark and Norway and Townsend fifth in Wales (S1a-c Tables).

When SES was examined as a linear trend, results were essentially unchanged. The decision to compare the most deprived with the rest was based on data in S5 and S6 Tables.

Numbers were too low for adjusted analyses in some anomalies of interest, including abdominal wall defects. In Wales, abdominal wall defects and SSRI exposure were associated with smoking and SES (S6 Table)[59].

^cUnadjusted analyses are reproduced here for the convenience of readers.

Confounding by indication:

a) Exposure patterns

Including only women present in the database from 1 year before to 1 year after pregnancy reduced the population (Fig 1), but left prevalence of anomalies and SSRI exposure largely unchanged. Prevalence was lowest in those never exposed, increasing in stoppers, pausers and those exposed during pregnancy: differences were not statistically significant. The prevalence of severe CHD was lower (0.23%) in those prescribed ≥1 SSRI prescription(s) in the 91 days either side of LMP than those receiving >1 prescription (0.31%) (Tables 6 S7).

Table 6. Comparisons of stopping before pregnancy, pausing during pregnancy, exposure LMP±91 days^a, and unexposed for 11 quarters for all anomalies, CHD and severe CHD, including receipt of >0 and >1 prescriptions: 3 countries

Exposed >0 SSRI prescription n=11,512								
	Unexposed 11 quarters ^b		Stoppers		Pausers		Exposed LMP±91 days	
	N	%	N	%	n	%	n	%
Total	426,962		6315		2203		11,512	
all anomalies	11,049	2.59	175	2.77	62	2.81	341	2.96
CHD	3651	0.82	64	1.01	24	1.09	94	0.82
severe CHD	722	0.16	9	0.14	4	0.18	26	0.23

Exposed >1 SSRI prescription n=6392								
	Unexposed 11 quarters*		Stoppers		Pausers		Exposed LMP±91 days	
	N	%	N	%	n	%	n	%
total	426,962		3146		923		6392	
all anomalies	11,049	2.59	87	2.77	26	2.82	190	2.97
CHD	3651	0.82	29	0.92	11	1.19	56	0.88
severe CHD	722	0.16	6	0.19	3	0.33	20	0.31

Notes: ^aExclusions as Table 1 plus 'not on database for 1 year either side of pregnancy'.

^b11 quarters - pregnancy and 1 year either side.

A full version of this table, with ORs and 95% CIs is available in Table S6. For all anomalies and severe CHD, differences between exposed to >1 SSRI prescription and unexposed yielded 95% confidence intervals excluding one.

b) Depression in Wales

For women present on the database during pregnancy and 1 year either side (n=103,204), a recorded diagnosis of depression (ever) was not associated with increased prevalence of all anomalies (OR 0.99, 0.89-1.10, Tables 7, S8). The prevalence of anomalies amongst those with a diagnosis of depression, medicated (3.22%) or unmedicated (3.19%), was slightly lower than following SSRI exposure, regardless of diagnosis (3.35%). More infants exposed to medicated than unmedicated depression had severe CHD, but numbers were small.

Table 7. Depression, medicated and unmedicated and congenital anomalies and stillbirths in Wales^a

	depression diagnosed (ever) n= 13189		no depression recorded n=90015			Depression exposed to N06AB LMP±91 days n= 2897		Depression un-medicated with N06AB* LMP±91 days n= 10292		
	N	% of diagnosed depressed	n	% of no depression recorded	OR (95% CI)	N	% of exposed	N	% of un-medicated	OR (95% CI)
Population	13,189	100	90,015	100		2897	100	10,292	100	
Anomaly or stillbirth	486	3.68	3158	3.51	1.05 (0.96-1.16)	108	3.75	378	3.67	1.00 (0.82-1.26)
aL1 All anomalies	422	3.20	2844	3.16	1.01 (0.91-1.12)	93	3.21	329	3.20	1.00 (0.79-1.27)
aL3 neural tube	10	0.08	97	0.11	0.70 (0.37-1.35)	<5		6-9		>1
aL17CHD	141	1.07	837	0.93	1.15 (0.96-1.38)	23	0.79	118	1.15	0.69 (0.44-1.08)
aL97Severe CHD	24	0.18	172	0.19	0.95 (0.62-1.46)	7	0.24	17	0.17	1.46 (0.61-3.53)
aL 49Abdo wall defects	16	0.12	60	0.07	1.82 (1.05-3.16)	<5		12-15		>1
aL50 gastroschisis	11	0.08	37	0.04	2.03 (1.04-3.98)	<5		7-10		>1
aL54 Renal dysplasia	9	0.07	68	0.08	0.90 (0.45-1.81)	<5		5-8		>1
aL59 Hypospadias	34	0.26	246	0.27	0.94 (0.66-1.35)	<5		30-33		>1
aL 61 Limb reduction	7	0.05	64	0.07	0.75 (0.34-1.64)	0		7	0.10	NA
aL66 talipes equinovarus	23	0.17	158	0.17	0.99 (0.64-1.51)	<5		19-22		<1
al 101: Oro-facial clefts	17	0.12	136	0.15	0.85 (0.52-1.41)	6	0.21	11	0.11	1.94 (0.72-5.25)

Notes: ^aExclusions and exposures as Table 1 plus 'not on database for 1 year either side of pregnancy'. Increased time on database was associated with a diagnosis of depression and increased deprivation, but not congenital anomalies, and correlation with maternal age was low (r= -0.06).

Values for any antidepressant (N06A) exposure are presented in S8 Table.

NA – unable to calculate. N06AB – any SSRI.

1 Deprivation was associated with depression and SSRI prescription (Table S5). We found no
2 significant associations between all anomalies, 'anomalies and stillbirths', CHD, severe CHD
3 and: smoking, substance misuse or heavy drinking, antipsychotics or deprivation. Abdominal
4 wall defects were associated with deprivation and smoking (S6 Table).

5
6 In subgroups of women recorded (ever) as heavy drinkers or substance misusers, the most
7 deprived fifth, those prescribed antipsychotics within 91 days of LMP, and smokers, SSRI
8 exposure increased the prevalence of congenital anomalies, particularly amongst heavy
9 drinkers or substance misusers (Table 8).

10

Table 8. Subgroup explorations in Wales: SSRI exposure and congenital anomalies or stillbirths^a

	SSRI exposure 91 days either side of LMP		
	SSRI exposed LMP±91 days n (% exposed)	Not SSRI exposed LMP±91 days n (% not exposed)	OR (95%CI) where available
Heavy drinking or substance misuse recorded (n=1658)			
Number	288	1370	
All Anomalies	18 (6.3)	38 (2.8)	2.34 (1.31-4.16)
CHD	6 (2.1)	13 (0.9)	2.22 (0.85-5.89)
Severe CHD	<5	<5	>1 (P>0.05)
Anomaly or stillbirth	19-22	44 (3.2)	>1 (<0.05)
Most deprived fifth (Townsend index of material deprivation) (n=25,763)			
Number	1910	23,853	
All Anomalies	70 (3.7)	781 (3.3)	1.12 (0.88-1.44)
CHD	19 (1.8)	235 (1.0)	1.01 (0.63-1.62)
Severe CHD	5 (0.3)	47 (0.2)	1.33 (0.53-3.35)
Anomaly or stillbirth	75 (3.9)	870 (3.6)	1.08 (0.85-1.37)
Exposed to any antipsychotic ^b at any time (n=833)			
Number	266	567	
All Anomalies	9/266 (3.4)	16/567 (2.8)	1.21 (0.53-2.77)
CHD	<5		<1 P >0.05
Severe CHD	<5		>1 P >0.05
Anomaly or stillbirth	10-13	17-21	>1 P >0.05
Smokers ^c (n= 30,534)			
Number	2583	27,951	
All Anomalies	92/2583 (3.6)	904/27,951 (3.2)	1.11 (0.89-1.38)
CHD	23/2583 (0.89)	265/27,951 (0.9)	0.94 (0.61-1.44)
Severe CHD	7/2583 (0.27)	49/27,951 (0.2)	1.55 (0.70-3.42)
Anomaly or stillbirth	110/2583 (4.3)	1019/27,951 (3.6)	1.18 (0.96-1.44)

Notes: ^aExclusions and exposures as Table 7.

^bFor antipsychotic and benzodiazepine exposure see S6 Table.

^cAlthough smoking was well recorded, some 15% women were classified as ex-smokers, with no cessation date; fieldwork experience indicates that some women self-report their smoking status as 'ex' when discontinuation has been <24 hours.

Amongst the 110 live birth cases of Down syndrome, exposure to SSRIs increased the incidence of CHD from 60/101 (60%) to 9/9 (100%) (RR 1.68, 1.43-1.98) [72].

Abdominal wall defects: too few cases to report.

Recorded recreational drug use was implausibly low, and not analysed.

Discussion

Congenital anomalies were more prevalent amongst infants exposed than unexposed to prescription of SSRIs within 91 days of 1st day of LMP, consistent with recent meta-analyses[26,30,73]. The confidence intervals excluded one for the composite adverse outcome of 'anomaly or stillbirth' (OR 1.13, 1.03 - 1.24, NNH 192). A dose-response relationship was found between SSRI prescription and 'anomaly or stillbirth' and severe CHD (meta-regression ORs 1.10, 1.02-1.20, and 1.49, 1.12-1.97), supporting work on paroxetine[34] and umbilical cord samples[74], but contrary to reports with fewer exposed cases[15], and different classifications[32].

The literature's inconsistency regarding SSRIs and CHD is reflected in our incongruent findings for all CHD and severe CHD. The dose-response association between SSRI prescription and severe CHD (Table 4) supports some studies[15,30,31], while the absence of association with all CHD reflects others[22,29,32,33]. As elsewhere, paroxetine was associated with all CHD and VSD[26,31,33], possibly attributable to its saturation kinetics[47]. Some reported associations were confined to a single SSRI: neural tube defects [33,35] with fluoxetine (OR 2.57, 1.21-5.46), escitalopram with talipes equinovarus[52], citalopram with hypospadias [27,75] (S3 Table S3). Genetic variation[76] and induction of the cytochrome P450 system, essential for SSRI metabolism, which occurs early in pregnancy, may reduce SSRI bioavailability and mitigate any adverse impact[51,77], particularly at standard doses.

Depression and social stressors are associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis, pro-inflammatory cytokines[78], and placental equivalents[79], which affect organogenesis[80], foetal growth[81], and birth outcome[82]. We found no association between anomalies linked with maternal social stressors (oro-facial clefts)[83] and SSRIs, antidepressants or depression (Tables S3, 7, S8). This intimates that independent serotonergic[11] and vasoconstrictor[9,50] mechanisms might underlie adverse outcomes following SSRI exposure [84]. SSRI-induced vasoconstriction[9,51] may explain associations between SSRIs and low birth weight, growth restriction[85-87], and persistent pulmonary hypertension[88], contributing to synergy in our composite adverse outcome. (Growth

1 restriction accounts for 43% of stillbirths [89]). Stillbirth is a relatively rare outcome
2 (prevalence <0.5%), not previously associated with SSRI exposure[90,91].

3
4 Adjusting for smoking and SES left findings largely unchanged (Table 5), as
5 elsewhere[16,28]. Exploration in Wales found no evidence for major confounding, except
6 for abdominal wall defects (S6 Table). Excluding subjects exposed to insulin, AEDs and
7 coumarins reduced the need to adjust for co-exposure[32]. SSRI prescription conferred
8 additional risks on those co-exposed to substance misuse or heavy drinking or other
9 psychoactive medicines[17,92-95] (Table 8).

10
11 To disentangle SSRI exposure from depression, like others [15], we compared those exposed
12 to SSRIs with those where prescriptions had been stopped or paused. Although prevalence
13 of ‘all anomalies’ and severe CHD was lower in those who stopped rather than continued
14 prescriptions, differences were not statistically significant, and confidence intervals were
15 wide, indicating limited power of this analysis or potential confounding (Tables 6 and S7). In
16 Wales, we analysed ‘any record of depression’, based on practitioners’ reluctance to repeat
17 data entries and the ‘depression diathesis model’, which suggests that any episode may
18 predispose to stressor-induced release of pro-inflammatory cytokines, permanently altering
19 hippocampal, prefrontal and frontocingulate neurochemistry and connections[78]. We
20 found no associations between depression and anomalies (Tables 7 and S8), supporting
21 suggestions that depression and antidepressants may act separately[84,96] in modifying
22 release of pro-inflammatory cytokines that affect organogenesis. Similarly, meta-analysis
23 indicates that increased risks of preterm birth persist when SSRI exposed are compared with
24 unmedicated controls diagnosed with depression [97]. Our definition of depression (any
25 record, ever) may contribute to incongruence with other reports[22,98]. We acknowledge
26 that prescription, resumption or higher doses of SSRIs may indicate on-going, recurrent or
27 more severe depression, compounding the difficulties of disentangling the effects of
28 prescriptions from underlying illness.

Strengths and limitations

Findings are strengthened by: precise diagnostic coding of congenital anomalies [37]; inclusion of TOPFA cases and stillbirths; contemporary controls; accounting for exposure to other antidepressants and SES; prospective data[99], free from recall bias [100]: these may explain differences with the published literature [15,16,24,32,33]. Most infants exposed to SSRIs in early pregnancy were not exposed in late pregnancy [3], reducing any over-ascertainment of anomalies in neonatal assessments of 'high risk' infants: the main concern is conflation of ASD with patent foramen ovale, which is precluded by EUROCAT coding [37]. Where associations were observed, effects were modest (ORs below 2), and the low numbers of exposed cases necessitate cautious interpretation, but the associations with severe CHD and 'major anomaly or stillbirth' are strengthened by dose-response relationships[101]. **Generalization** of findings on 'all anomalies', with or without stillbirths is strengthened by consistency across different populations ($I^2=0$ for both analyses) (Tables 3 and S3). Our findings are limited by: dilution of exposure; incomplete recording in electronic databases; and study size.

Our **effect sizes** may be conservative and ORs diluted by our extended exposure window, and threats to prescription adherence. Our extended time window before LMP (91 days) was based on typical prescription duration and pharmacokinetic parameters, which differ between SSRIs. We acknowledge that this may have led to some unexposed subjects being misclassified as exposed, diluting ORs [102], particularly for SSRIs with shorter half-lives (citalopram, sertraline, escitalopram, and low dose paroxetine)[47], possibly explaining divergent findings[16,32,103].

Adherence to prescribed regimens cannot be ascertained from prescription or dispensing data. However, it is more likely where >1 prescription is issued, and therefore our stronger findings when analysing women exposed to >1 prescription are consistent with dilution due to exposure misclassification from non-adherence. International differences in exposure observed may, in part, reflect differences in issued (Wales) versus redeemed (Norway, Denmark) prescriptions. Prescription non-redemption varies between settings; reviewers

suggest a mean of 16.4% (range 11-19%)[104]. For antidepressants, estimates range from 20% in the USA where affordability is a prominent concern[105], to 4% in the Netherlands [106] and 4.5% (CNS medicines) in UK primary care [107].

Electronic cohorts based on prospectively collected routine data facilitate pharmacovigilance across whole populations; however, clinical details (other than EUROCAT coding) including indications for prescriptions and severity of illness, confounding variables and genotype may be incompletely recorded. Dose-response explorations were based on tablet size, and we were unable to take account of formulation or number of tablets or packets prescribed. Genetic vulnerability to environmental factors, including SSRIs, is hypothesised[76], but rarely recorded. Some anomalies, including some not associated with recognised syndromes, can result from inherited conditions[108]. However, family histories tend to be incompletely recorded, and there may be no information on fathers and other family members, including any paternal half-siblings. Information on paternity is also difficult to obtain in fieldwork[109]. CHDs are associated with maternal CHD[58], and even a small number of affected women might affect our interpretation of the severe CHD outcome. Although we checked as thoroughly as possible, data on maternal morbidities were limited by timeframes of databases and, possibly, incomplete recording. We did not exclude women with: diabetes not prescribed insulin, unmedicated epilepsy, glucose-6-phosphate dehydrogenase deficiency, sickle cell anaemia, maternal hypertension. BMI was poorly recorded in all databases, precluding exploration of confounding by obesity[110].

Recreational drug use, heavy alcohol use and substance misuse are captured poorly in clinical care, fieldwork and databases. These potential confounders were not available in the Scandinavian databases. Only problems recorded by primary care professionals could be identified in Wales; this would not include casual users or regular users not reporting problems. Depression may be under-reported in primary care records, due to inaccurate diagnosis by primary care practitioners[111], fears of 'labeling' or stigmatizing[112], and, possibly, incomplete record transfer from secondary care. Accordingly, we acknowledge the risks of under-ascertainment, and the limitations of taking the absence of any records as indicative of non-exposure. Adjustment was limited by low numbers of exposed cases, incomplete recording of smoking (Table S1a-c, 6 and S7) and, in Denmark, a higher

prevalence of missing data amongst cases (S1a-c Tables). However, in Wales, alternative predictors were not identified for anomalies other than abdominal wall defects (S6 Table).

Analyses of all antidepressants and SSRIs excluding co-prescription of other antidepressants could not include Denmark, and therefore are not directly comparable to the main results.

The study's size was sufficient (>312,000) to detect an association between SSRI exposure (2.50%) with major anomalies (prevalence 2.68%, Table 1) greater than OR 1.2, with 80% power and alpha 0.05, but >1,000,000 subjects would be needed to detect ORs of 1.1. For the commonest anomaly, CHD (prevalence 0.9%) and the commonest SSRI (citalopram, 0.8% exposure), there were sufficient subjects (>456,000) to detect an OR of 1.5 [113]. Higher prescription rates in Wales gave more exposed pregnancies (and power) than previous cohorts[14,21] benefitting from verified EUROCAT coding[15,22,33].

We acknowledge the hazards of **multiple testing**, without correction, but recognise the tensions between umbrella terms, which can hide true signals between specific anomalies and specific medicines, and narrow categories or rare outcomes yielding numbers too small for statistical comparisons[114,115]. *A priori* hypotheses[9,27,31,35,51] were tested without statistical adjustment, to limit misinterpretation (Table 3)[116]. Associations between individual agents and anomalies offer signals for replication in independent data sets (S3 Table). Our population-based cohort study yielded lower ORs than Wemakor *et al's* [31] case-malformed control study of 12 EUROCAT registries, suggesting that we have not over-estimated harms, congruent with reports that estimates of adverse event rates are lower in cohort than case-control studies[117].

Logical and biological inferences should be considered when interpreting these findings, which are congruent with seven of the nine Bradford-Hill criteria of causation [118]: temporal and dose-response relationships; consistency of effect size (ORs) for 'all anomalies' internally, and with the literature[26,30,73]; biological plausibility; consideration of alternative explanations (depression, SES, smoking); specificity to severe CHD; and coherence with extant theories of serotonergic transmission and vasoconstriction. However, neither we nor others offer experimental evidence, and the associations, while persistent

and clinically serious [53], represent small absolute risk differences (Table 3). Where partial overlap between our data and that published by EUROCAT[31], the Danish 1995-2008[103], and Nordic authors 1996-2010[16] occurs, findings are consistent. However, the last excluded stillbirths and TOPFAs, reducing the prevalence of anomalies. We have avoided P values, but acknowledge the problems inherent in dichotomizing data according to 95% confidence intervals where assignment is not randomized and assumptions (for example on adherence) are unverifiable [119]: interpretation and translation into clinical practice rest with readers.

Interpretation and care pathways

Our findings resonate with larger cohorts and meta-analyses[26],[30],[73], despite the risks of attenuation of odds ratios, above. SSRI prescription in the 91 days either side of LMP was associated with higher prevalence of anomalies and stillbirths: ~7 rather than ~6 adverse outcomes per 200 exposed births. The heterogeneity in severe CHD may be attributable to diverse prescription regimens, environmental factors or ill-defined contextual variables. The higher prevalence was most apparent in Denmark, where single prescriptions were unusual and high doses relatively common, and absent in Norway, where single prescriptions were more common, high doses and paroxetine relatively rare, and escitalopram the most popular SSRI. The UK formulary [120] notes the pro-arrhythmic potential of escitalopram and contra-indicates breastfeeding, which may explain lower use in Wales.

Antidepressant use in pregnancy is determined by the balance between benefits to the woman and harms to the foetus: there is no certainty that realisation of the fourth (reducing child mortality) and fifth (improving maternal health) UN Millennium Development goals[121] will always coincide. Congenital anomalies and stillbirths are not the only harms associated with antidepressants[122]. Prescribing decisions are informed by other possible harms[73,123]: spontaneous abortion[29,124], low birth weight, prematurity, admission to neonatal special care facilities [33,85-87,125], gestational hypertension, postpartum haemorrhage[126], persistent pulmonary hypertension in neonates[88,120,127,128], concerns over delayed motor development[129].

1 The uncertain clinical effectiveness of antidepressants in pregnancy[126,130] for mild or
2 moderate depression[131,132], treatment resistance in some 30% patients[78], contra-
3 indication in mild depression [120], and wide variations in prescribing across Europe[3]
4 underlie recommendations to restrict pharmacotherapy in pregnancy to women with severe
5 depression[133-135] or adjust prescribing thresholds[73]. However, poor parental perinatal
6 mental health can adversely affect childhood outcomes [136], while effects on perinatal
7 outcomes are modest [137], and more marked in developing countries [138]. Guidelines'
8 equivocation places the onus on prescribers [139,140], despite constraints in primary care,
9 including short appointment times[141]. Withholding or withdrawing antidepressants from
10 women with serious illness may worsen illness or induce withdrawal symptoms or
11 relapse[133,142], and clinicians are mindful of the increased risk of harm, including suicide,
12 in the 28 days following discontinuation[143], but more evidence relating to those less
13 seriously ill is needed. With high exposure rates (>5% in Wales), many women fall into the
14 latter category, who may derive less benefit from SSRIs, whilst risking the same harms.

16 **Implications**

17 The clinical importance of stillbirth and major congenital anomalies, including severe CHD,
18 suggests that small increases in absolute risk might influence decisions on therapy and care
19 pathways at population level[144]. Examination of three Northern European population
20 cohorts consistently indicated an association between SSRIs and major anomalies, which
21 increased when stillbirths were included. Uniquely, the association identified with severe
22 CHD was supported by: a dose-response relationship, lower prevalence in those stopping
23 SSRIs, higher prevalence in those with >1 prescription, minimal confounding by SES, plus, in
24 Wales, no association with alternative exposures, including depression. Given the rarity of
25 specific congenital anomalies and ethical considerations, randomised trials with these
26 outcomes may never be undertaken. However, since risk estimates for adverse events are
27 similar in trials and observational studies[145], these findings have implications for practice.
28 Even if associations reported here are not necessarily causal, SSRI prescriptions can be
29 identified in primary care records and offer convenient, markers for increased vulnerability,
30 more easily ascertained and reliable than smoking status or recreational drug consumption
31 [109,146]. Balancing the number needed to harm, 192, with the severity of potential

adverse effects (stillbirth or major anomaly) [53], whilst minimising any iatrogenic harm [140] might entail regarding records of SSRI prescriptions as indication to:

- Target all women contacting primary care for SSRI prescriptions, not just those identifying themselves as planning pregnancy, since ~43% UK pregnancies are unplanned[147].
- Regard substance misuse or heavy drinking as possible indicators of high risk from SSRI prescribing (6.3%).
- Expand pre-conception care to include: reviewing therapeutic regimens, *particularly high doses of SSRIs*; reflecting that ~40% women discontinuing SSRIs after conception do not restart within a year of childbirth [3], and cognitive behavioural therapy may be equally effective[148]; prescribing folic acid, which may reduce the prevalence of CHD[149].
- Consider offering women prescribed SSRIs in pregnancy 24-26 week and third trimester scans or alternative continuous monitoring technology to:
 - take advantage of advances in monitoring and surgery *in utero*
 - ensure appropriate levels of neonatal care are available at birth.
- Consider offering a modified care pathway to include detailed ultrasound scans with views of the 4 cardiac chambers, outflow tracts and aortic arch plus Doppler investigation of blood flow[150].

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Supporting Information

Appendix 1: supplementary tables

Tables S1a-c the populations

Tables S2a and 2b Anomalies and exposures for each SSRI and all antidepressants

Table S3 anomalies and SSRI exposure for each agent with data from 3 countries

Table S4 anomalies and SSRI exposure with and without antidepressants

Table S5 Deprivation and selected exposures in Wales

Table S6. Exploration of anomalies and alternative exposures in Wales

Table S7. Comparisons of stopping before pregnancy, pausing during pregnancy, exposure LMP \pm 91 days, and unexposed for 11 quarters for all anomalies, CHD and severe CHD, including receipt of >0 and >1 prescriptions: 3 countries

Table S8. Depression, medicated and unmedicated and congenital anomalies and stillbirths in Wales^a

Appendix 2 STROBE statement

Statements and Declarations

Funding

Financial support for the EUROMediCAT study was provided by the European Union under the 7th Framework Program (grant agreement HEALTH-F5-2011-260598). Start date: 1 March 2011. Duration: 48 months. *Coordinator* Prof. Helen Dolk, University of Ulster, UK Tel: +44 28 90368540, Email: h.dolk@ulster.ac.uk. Further information can be found at www.euromedicat.eu

The funder played no part in the study or production of the paper and the research report.

Acknowledgements

This study uses anonymised data held in the Secure Anonymised Information Linkage (SAIL) system, which is part of the national e-health records research infrastructure for Wales. We should like to acknowledge all the data providers who make anonymised data available for research. Data held in SAIL databases are anonymised and aggregated and have been obtained with permission of relevant Data Protection Officers, as approved by the National Research Ethics Service, Wales. EUROMediCAT was approved by the SAIL Information Governance Review Panel (IGFRP) on 24th March 2011. Since EUROMediCAT uses only anonymised data, ethical review was deemed unnecessary.

The EUROMediCAT project was given approval from the Norwegian Data Inspectorate on 12th February 2013 (12/00617-4/EOL), and from the Regional Committee for Medical and Health Research Ethics, North on 5th June 2012 and 7th July 2015 (2012/757/REK nord).

We should like to thank: Hildrum Sundseth from the European Institute of Women's Health and Geoff Adams-Spink from the Thalidomide Society for their advice on the project; Anne-Marie Nybo Andersen, Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark, for use of data and input; Vivian Morgan, Public Health Wales, for administrative support.

Details of ethics approvals

Wales: The EUROMediCAT project was given approval from the SAIL/ HIRU Information Governance Review Panel (IGFRP) on 24th March 2011.

1 Norway: The EUROmediCAT project was given approval from the Norwegian Data
2 Inspectorate on 12th February 2013 (12/00617-4/EOL), and from the Ethical Committee for
3 Research on 5th June 2012 and 7th July 2015 (2012/757/REK nord).
4 Funen, Denmark: Linkage of databases for the EUROmediCAT project was approved by the
5 Danish Data Inspection Agency on May 27.th 2011 (2011-231-0098)

6 7 **Declarations of interest**

8 All authors have declared that they have no competing interests.
9

10 **Data sharing:**

11 Additional data are available in the EUROmediCAT report and its appendices. No patient level data
12 are available under the terms of ethical and governance reviews. No participant consent is obtained
13 for population level studies. The corresponding author will endeavour to meet requests for further
14 data.
15

16 The study used data from three databases. Individual records for all databases were anonymised,
17 and individual patient data cannot be publicly deposited or fully shared upon request. They are only
18 available directly from the database providers where appropriate. All other interested parties are
19 able to apply to obtain the data in the same way as the current investigators.
20

21 **Contributorship:**

22 HD, SJ, EG, JM designed the study. IDG, DST, AVH, AE, KK, DT, MM, BB collected,
23 analysed and linked the data. JM & JL undertook statistical analyseis with input from all
24 authors. SJ drafted the manuscript. All authors contributed to the final draft.
25